

Patent Claims:

1. A bispecific antibody, or a fragment thereof, having the capability to bind to different epitopes located on same or different ErbB receptor molecule types, said antibody comprising a first antigen-binding site that binds to an epitope of a first receptor type, which is ErbB1, and a second different antigen-binding site that binds to a different epitope of a second ErbB receptor molecule type.
2. A bispecific antibody according to claim 1, wherein said second ErbB receptor molecule type is ErbB1 (EGFR).
3. A bispecific antibody according to claim 1, wherein said second ErbB receptor molecule type is ErbB2 (Her-2).
4. A bispecific antibody according to any of the claims 1 – 3, wherein at least one of said epitopes is located within the receptor binding domain.
5. A bispecific antibody of claim 4, wherein said receptor binding domain is the binding domain of the natural ligand(s) of said ErbB receptor.
6. A bispecific antibody according to any of the claims 1 – 3, wherein the first or second antigen binding site binds to an epitope within the binding domain of the natural ligand(s) of said ErbB receptor molecule type.
7. A bispecific antibody according to any of the claims 1 – 3, wherein the first and second antigen binding site binds to an epitope within the binding domain of the natural ligand(s) of said ErbB receptor molecule type.
8. A bispecific antibody according to any of the claims 1 – 7, wherein the antigen binding sites bind to different epitopes which are located on the same ErbB receptor molecule type.

9. A bispecific antibody according to any of the claims 1 – 7, wherein the antigen binding sites bind to different epitopes which are located on different ErbB receptor molecule types.
- 5 10. A bispecific antibody of claim 8, wherein the first and second antigen binding site binds each to a different epitope within the binding domain of the natural ligand of said ErbB receptor, thus blocking and / or inhibiting the receptor, whereby blocking and / or inhibition of the ErbB receptor, and induction of down-regulation of ErbB receptor-specific pathway signaling is enhanced as compared
10 with the respective monospecific antibody.
11. A bispecific antibody of claim 9, wherein induction of crosslinking and / or dimerization of different ErbB receptor molecules having the same or different specificity, is enhanced as compared with binding of the bispecific antibody to
15 epitopes on the same ErbB receptor molecule..
12. A bispecific antibody according to any of the claims 1 – 11, wherein said first antigen-binding site derives from humanized, chimeric or murine MAb 425.
- 20 13. A bispecific antibody according to any of the claims 1 – 11, wherein said first antigen-binding site derives from humanized, chimeric or murine MAb 225.
14. A bispecific antibody according to claim 12 or 13 designated as "BAb <h425, c225>", wherein said first antigen-binding site derives from humanized, chimeric
25 or murine MAb 425, and said second antigen-binding site derives from humanized, chimeric or murine MAb 225, and each antigen-binding site binds to a different epitope on the ErbB1 receptor (EGFR) molecule.
15. A bispecific antibody of claim 14, wherein said different epitopes are located
30 within the binding domain of the natural ligand(s).
16. A bispecific antibody according claim 12 or 13, wherein the second antigen binding site binds to a ErbB2 receptor molecule (Her-2) or a VEGF receptor molecule.

17. A bispecific antibody of claim 16, wherein said second antigen-binding site derives from MAb 4D5 (Herceptin®).
18. A bispecific antibody fragment deriving from a bispecific antibody as defined in
5 any of the claims 1 – 17, wherein the fragment is F(ab')₂.
19. An immunoconjugate comprising a bispecific antibody according to any of the claims 1 – 18 or a fragment thereof, fused directly or via a linker molecule via its C-terminus to a biologically effective protein, polypeptide or peptide.
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20. An immunoconjugate of claim 19, wherein said protein is a cytokine.
21. A pharmaceutical composition comprising a bispecific antibody or an immunoconjugate as specified in any of the claims 1 – 20, optionally together
15 with a pharmaceutically acceptable carrier, diluent or excipient.
22. A pharmaceutical composition of claim 21, further comprising a monospecific anti-ErbB antibody or a functionally effective fragment thereof.
- 20 23. A pharmaceutical composition of claim 22, wherein said monospecific anti-ErbB antibody or a functionally effective fragment thereof is selected from the group consisting of MAb 425, MAb 225, or MAb 4D5 (Herceptin®).
24. A pharmaceutical composition according to any of the claims 21 – 23, additionally
25 comprising a cytotoxic agent.
25. A pharmaceutical composition according to claim 24, wherein said cytotoxic agent is a chemotherapeutic agent.
- 30 26. A pharmaceutical composition according of claim 25, wherein said chemotherapeutic agent is selected from any of the compounds of the group: cisplatin, doxorubicin, gemcitabine, docetaxel, paclitaxel, bleomycin.

27. A pharmaceutical composition of claim 24, wherein said cytotoxic agent is an ErbB receptor inhibitor, a VEGF receptor inhibitor, a tyrosine kinase inhibitor, a protein kinase A inhibitor, an anti-angiogenic agent, an anti-hormonal agent, or a cytokine.
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28. A pharmaceutical kit comprising
- (i) a first package comprising at least a bispecific antibody or an immunoconjugate, as specified in any of the claims 1 to 20, and
- (ii) a second package comprising at least a monospecific anti-ErbB antibody or a functionally effective fragment thereof.
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29. A pharmaceutical kit according to claim 28 comprising a first package that comprises bispecific antibody "BAb <h425, c225>" or its F(ab')₂ fragment, and a second package comprising humanized MAb 425 (h425), chimeric MAb 225 (c225) or humanized MAb 4D5 or functionally effective antibody fragments thereof.
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30. A pharmaceutical kit according to claim 28 or 29 comprising additionally a third package comprising a cytotoxic drug.
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31. A pharmaceutical kit according to claim 30, wherein said cytotoxic drug is selected from any of the compounds of the group: cisplatin, doxorubicin, gemcitabine, docetaxel, paclitaxel, bleomycin, an ErbB receptor inhibitor, a VEGF receptor inhibitor, a tyrosine kinase inhibitor, a protein kinase A inhibitor, an anti-hormonal agent, or an anti-angiogenic agent.
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32. Use of a bispecific antibody or a pharmaceutical composition / kit as defined in any of the claims 1 – 31, for the manufacture of a medicament for the treatment of tumors and tumor metastases and related diseases that overexpress ErbB receptors.
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